

# Aortic and mitral bioprosthetic valve dysfunction: surgical or percutaneous solutions?

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## KEYWORDS

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In the last years, there has been a trend to prefer biological prostheses, especially among young patients, with the aim to avoid anticoagulant treatment. Surgical tissue valves have so far demonstrated their solid long-term durability. However, younger age has been identified as one of the main risk factors for developing structural valve deterioration (SVD). As a consequence, the proportion of subjects at risk for valve dysfunction will constantly rise in the near future. However, while surgical reintervention has always been considered the gold standard for treatment of prosthesis deterioration, the introduction of transcatheter heart valves could offer new therapeutical options, particularly among high-risk patients, aiming a second less invasive chance. The recent standardization of valve durability definitions will soon allow a more comprehensive understanding of the mechanism underlying SVD and guide the choice of prosthesis for patients needing valve replacement.

## Introduction

The choice between biological vs. mechanical prosthesis has always been challenging. Nowadays, patients are more accepting the idea of reoperation rather than the need for life-long anticoagulation. However, despite improvement in anti-mineralization processes, biological tissue remains subject to degeneration. We are still far from the discovery of the ‘ideal’ biological prosthesis. On the other side, repeated surgery is not the only solution anymore: introduction of percutaneous valve procedures has been established as an efficient alternative to treat deteriorated bioprostheses, although long-term results are still missing. How this innovation affects the decision-making in the current era?

## The growing use of biological valve prostheses

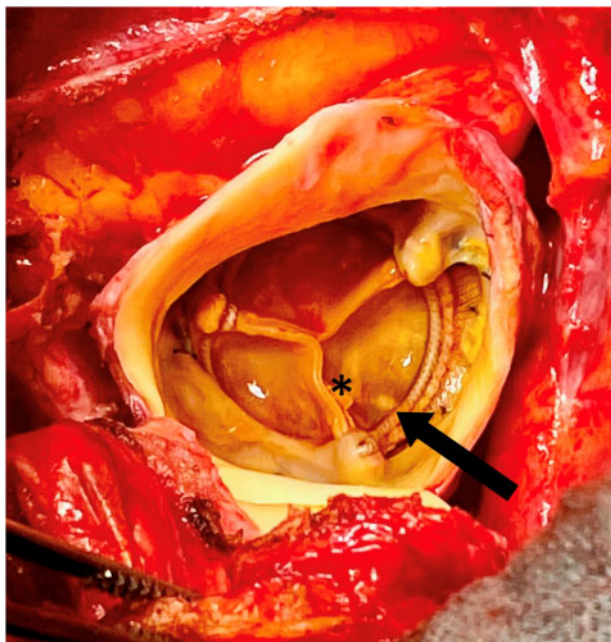
By 2050, it is expected that the annual number of patients undergoing heart valve replacement will triple from

approximately 290 000 in 2003 to over 850 000.<sup>1</sup> A growing part of these patients will probably choose a tissue valve. The age threshold for tissue valves has been lowered (even in the guidelines), mainly because younger patients are attracted by the possibility of avoiding lifelong anticoagulant therapy. The reduction of the reoperation risk, as well as an increased awareness of anticoagulation complications, may explain the constant trend towards bioprosthetic choice over mechanical valves. As a result, in the New York state, the proportion of biologic prostheses implanted among patients between 50 and 70 years of age has increased in the last two decades from 15% to 74% and from 8% to 60% for the aortic and mitral position, respectively.<sup>2,3</sup>

## A new definition for valve degeneration: how to assess durability?

Historically, the definition of durability consisted in ‘freedom from reintervention for valve dysfunction’, a parameter which unfortunately may underestimate the true incidence of valve deterioration, especially in asymptomatic patients and in high-risk patients who are not

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**Figure 1** Bioprosthetic structural valve deterioration. A degenerated surgical stented biological prosthesis (Carpentier-Edwards Perimount). The arrow indicates a fibrocalcific plaque, while asterisk highlights a leaflet thickening and partial tear.

considered for reintervention. In the last years, dozens of definitions have been adopted in the literature, including a variety of echocardiographic criteria. This wide range of definitions lead to confusion and impeded homogeneous comparisons.

To overcome this issue, in 2017, Capodanno *et al.*<sup>4</sup> reported a consensus statement on standardized definitions of structural deterioration and valve failure endorsed by the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the European Society of Cardiology (ESC), and the European Association for Cardio-Thoracic Surgery (EACTS). This document introduces a new classification for bioprosthetic valve dysfunction (BVD) that embraces four principal types of abnormal functions: structural valve deterioration (SVD), non-structural valve deterioration (NVD), thrombosis, and endocarditis. SVD should be defined as a permanent intrinsic change of the tissue component of the valve (i.e. leaflet tear, calcification, flail etc.) leading to degeneration and/or dysfunction which in turn may result in stenosis or intra-prosthetic regurgitation (*Figure 1*). According to this definition, causes of potentially reversible dysfunction (i.e. thrombosis and endocarditis) are excluded. Deterioration events unrelated to the valve itself were included among the NVD category: this incorporates ‘any abnormality not intrinsic to the prosthetic valve itself leading to degeneration and/or dysfunction’, such as paravalvular leak (PVL), prosthesis malposition, patient-prosthesis mismatch (PPM), and late embolization. SVD is furtherly defined as *haemodynamic* or *morphological*. The first refers to clinically relevant and permanent haemodynamic changes of the valve function assessed by echocardiography, which could be classified as moderate and severe, even without evidence of

morphological abnormalities. The second one is still based upon imaging findings but suggests alterations of leaflet integrity (i.e. flail), structure (i.e. thickening), function (i.e. impaired mobility), or frame (i.e. strut fracture). The consensus statement introduces a revolutionary definition: bioprosthetic valve failure (BVF). BVF is a condition in which valve dysfunction of any source (beyond just SVD) plays a relevant role in the clinical status of the patients. Therefore, the definition of degeneration moves from a mere prosthesis-oriented binary outcome to a proper patient-centred endpoint, focused on the clinically meaningful consequences. Actually, what patients care the most is the risk of death, reintervention and severe symptoms, rather than the evidence of SVD.

Another addition to the management of SVD is the 2018 Valve-in-Valve (ViV) consensus document proposing a staging model of SVD. The document proposes clinical management recommendations according to the stage of bioprosthetic degeneration (*Table 1*).<sup>5</sup>

Regardless of the classification method, it appears undebatable that periodic transthoracic echocardiography (TTE) represents the gold standard imaging modality to identify the SVD stage.<sup>6</sup> All patients after surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) should undergo a postprocedural TTE (within 30 days) to provide a baseline analysis for comparison, particularly helpful for differential diagnosis against PPM. Thereafter, a yearly echocardiographic follow-up is deemed mandatory,<sup>7</sup> providing the echocardiographer applies an advanced knowledge of prosthesis design for an inclusive analysis. Albeit not routinely performed, cardiac computerized tomography (CT) could add pivotal information, remarkably when prosthetic thrombosis is suspected, since the presence of hypoattenuated leaflet thickening could reveal subclinical forms of thrombotic layer appositions generating hypomobility of the leaflets, eventually associated with early signs of degeneration.

### Degeneration below the surface

Macroscopically, SVD develops when the bioprosthetic cusps become thickened and stiffer, due to apposition of fibrocalcific plaques and collagen disruption. In some occasions, tissue degeneration develops with leaflet tears or perforations. Despite 0.6% glutaraldehyde fixation to stabilize the cell membrane, implanted tissue valves are subject to continuous mechanical stress, increased by hypertension, which could lead to membrane damage and, thus, to nucleation of calcium crystals. In addition, the presence of residual xenograft antigens is associated with a marginal immune response, as well as to an atherosclerotic process mediated by oxidized lipids and macrophages metalloproteinases.<sup>8</sup> Furthermore, it is current opinion that both healed endocarditis and valve thrombosis, even subclinical, could lead to accelerated SVD mediated by inflammatory activity. As a consequence, many causes could accelerate SVD, including patient-related (i.e. sex, younger age, diabetes, hypercholesterolaemia, increase plasma apo-B/apo-A lipoprotein ratio, kidney disease, hyperparathyroidism) and prosthesis-mediated factors (i.e. small

**Table 1** Structural valve deterioration staging

Stage	Definition	Echo parameter	Management
0	Normal function	Normal echo parameters	Clinical + TTE yearly
1	Morphological leaflet abnormalities	No significant changes in haemodynamic valve function	TTE at 3-6 months; trial of anticoagulation if subclinical leaflet thrombosis is suspected
2	Moderate haemodynamic dysfunction	Mean gradient 20-40 mmHg, or 10-20 mmHg change from baseline, or moderate AR	Clinical + TTE at 3-6 months; consider re-intervention if symptomatic for SVD
3	Severe haemodynamic dysfunction	Mean gradient $\geq 40$ mmHg, <sup>a</sup> or $\geq 20$ mmHg change from baseline, or severe AR	Consider reintervention; if asymptomatic with preserved LVEF consider clinical + TTE every 3-6 months

The table resumes definition and principal echocardiographic parameters to define SVD staging and its clinical management according to the degree of degeneration.<sup>3</sup> Baseline post-implant TTE and at 30 days is recommended.

AR, aortic regurgitation; LVEF, left ventricular ejection fraction; SVD, structural valve deterioration; TTE, transthoracic echocardiography.

<sup>a</sup> $\geq 30$  mmHg following latest VARC-3 definition.

prosthesis size resulting in severe PPM, inadequate antimicrobialization).

### Surgical tissue valve degeneration: a long, but inexorable process

Among the spectrum of surgical bioprostheses launched on the market in the past 30 years, the issue of which valve type performs better has been long debated. Currently, pericardial stented valves have shown the most promising results in terms of long-term durability. Bourguignon *et al.*<sup>9,10</sup> analysed long-term durability of the Carpentier-Edwards Perimount pericardial bioprosthesis on 2758 and 148 patients in the aortic and mitral position, respectively. The authors reported rates of freedom from explant due to SVD of  $54 \pm 5\%$  and  $25 \pm 8\%$  at 20 years for the aortic and mitral valve, respectively. The rate of SVD explant described by Johnston *et al.*<sup>11</sup> on more than 12 500 patients undergoing SAVR with the Carpentier-Edwards Perimount prosthesis was 15% at 20 years. Risk analysis showed that early explants are usually related to endocarditis, while the SVD phase starts at 5 years and increases sharply 10 years after surgery. However, not all surgical bioprostheses behave similarly: the pericardial Mitroflow valve revealed a tendency for early SVD, while stentless prostheses (i.e. Sorin Freedom), which initially have shown promising haemodynamic outcome, appear less durable than the stented one and vulnerable to extensive calcifications. Interestingly, while previous studies reporting freedom-from-reoperation may suggest valve durability beyond 15 years, data from the VIVID registry shows that most ViV procedures for failed surgical aortic valves occurs around 9 years post-SAVR. The VIVID registry offers a real-world insight on surgical bioprostheses longevity, although might underestimate a tendency towards early and more liberal reintervention with the percutaneous approach (ViV).<sup>12</sup>

When durability relates to the mitral valve, the debate on choice of bioprosthetic type is still ongoing. In a recent meta-analysis including more than 15 000 patients who underwent surgical mitral valve replacement (SMVR),

porcine valves had a higher freedom from SVD at 15 years as compared to the pericardial ones. SVD rates of the porcine prostheses (Carpentier-Edwards porcine, Hancock II, Mosaic) and Carpentier-Edwards pericardial valves were 67-80% and 61%, respectively ( $P < 0.001$ ).<sup>13</sup>

In the mitral position, bioprosthetic valves are expected to degenerate faster than on the aortic side. For this reason, a higher age limit for tissue prostheses in mitral position has been recommended by the latest guidelines (age  $>70$  years old vs. 65 years old for the aortic position).<sup>7</sup> However, recent evidence shows that the long-term mortality benefit associated with a mechanical prosthesis in aortic position persists only until 55 years, therefore current age-related cut-offs may be even lowered.<sup>14</sup> Nevertheless, younger age is a well-established predictor of SVD. At 20 years from surgery, cumulative incidence of explant for SVD was 45% in patients younger than 60 years and only 8% for those with  $>60$  years old.<sup>11</sup> It must be however noted that the younger the age the less the impact of the mortality as competing factor influencing the rate of clinically relevant degeneration.

With the introduction of the ViV concept, the overall debate on durability and the choice of prosthesis has changed dramatically: the possibility of a second or even third reintervention with a percutaneous approach opens the perspective of a life-time tissue valve strategy even in young and low-risk patients, although some challenges are associated with this idea (see below).

### Are transcatheter valves as durable as the surgical ones?

Most experts in the field predicted that transcatheter heart valves (THVs) would provide shorter durability as compared to that expected from the surgical ones. Surgical valve durability improved over the years, thanks to multiple developments in design, manufacture, quality control, and tissue treatment.

THV durability has been expected to be shorter than the one observed in the surgical valves due to several technical

aspects such as microscopic tissue damage related to crimping, the lack of annular decalcification, under/over-expansion and implantation height that could alter THV geometry and stress tolerance. Given all these reasons, some concerns have been raised about reliability of THV longevity, although current data looks promising, especially when compared with surgery.

Differently from surgical prosthesis durability data, based on several decades of follow-up for some prostheses, current THVs longevity evidence is limited to 5-8 years. In addition, the patients treated with TAVI in the early days were elderly and comorbid subjects in which the competing risk of death could lead to an underestimation of the risk of SVD. In addition, most of the recent randomized clinical trials (RCTs) in intermediate-risk patients excluded the younger population, in which SVD is more common.

Despite similar BVD rates between TAVI and SAVR (TAVI 56.1% vs. SAVR 66.7%,  $P=0.073$ ), the NOTION trial, which includes 100% first-generation CoreValve, showed a higher 6-year rate of SVD in the surgical than in the percutaneous arm (4.8% vs. 24.0%,  $P<0.001$ ).<sup>15</sup> Contrarily, a similar incidence of NVD (54.0% vs. 57.8,  $P=0.52$ ) and endocarditis (5.8% vs. 5.9%,  $P=0.95$ ) were reported. Among the patients which developed NVD, TAVI group revealed more post-procedural moderate PVL (20.9% vs. 1.5%,  $P<0.0001$ ), but less severe PPM at 3 months (12.2% vs. 28.1%,  $P=0.001$ ), compared to SAVR. Interestingly, when analysing the patient-oriented outcome, similar rates of BVF were reported (7.5% vs. 6.7%,  $P=0.89$ ). The incidence of valve-related deaths (5.0% vs. 3.7%,  $P=0.59$ ), reintervention (2.2% vs. 0.7%,  $P=0.62$ ), and severe haemodynamic SVD (0.7% vs. 3.0%,  $P=0.21$ ) was comparable in the two groups.

## Therapeutical options

Currently, surgical reinterventions can be performed with acceptable mortality, despite some categories are at increased risk of death such as older patients, those who previously underwent coronary artery bypass graft and those who presented non-electively with endocarditis, valve thrombosis or PVL.

In 2015, the multicentre European RECORD study included 711 patients who underwent redo SAVR for various indications and showed a perioperative mortality of ~5%.<sup>16</sup> Reduced left ventricular ejection fraction (<30%), advanced functional New York Heart Association class (III-IV), double valve surgery, renal failure, and prolonged cardiopulmonary bypass time predicted in-hospital death. Morbidity rates were high: 15% of patients developed low cardiac output syndrome, 7% stroke, 11% acute respiratory failure, and 19% acute kidney injury. Incidence of blood transfusion (67%) and pacemaker (PM) implantation (13%) were elevated as well. Mid-term 3-year follow-up revealed a survival rate of 77%.

On the other hand, the international VIVID registry has collected promising results with the percutaneous treatment of degenerated surgical bioprostheses during the last decade.<sup>12</sup> In this registry, 459 patients with degenerated aortic surgical bioprosthesis underwent a ViV procedure,

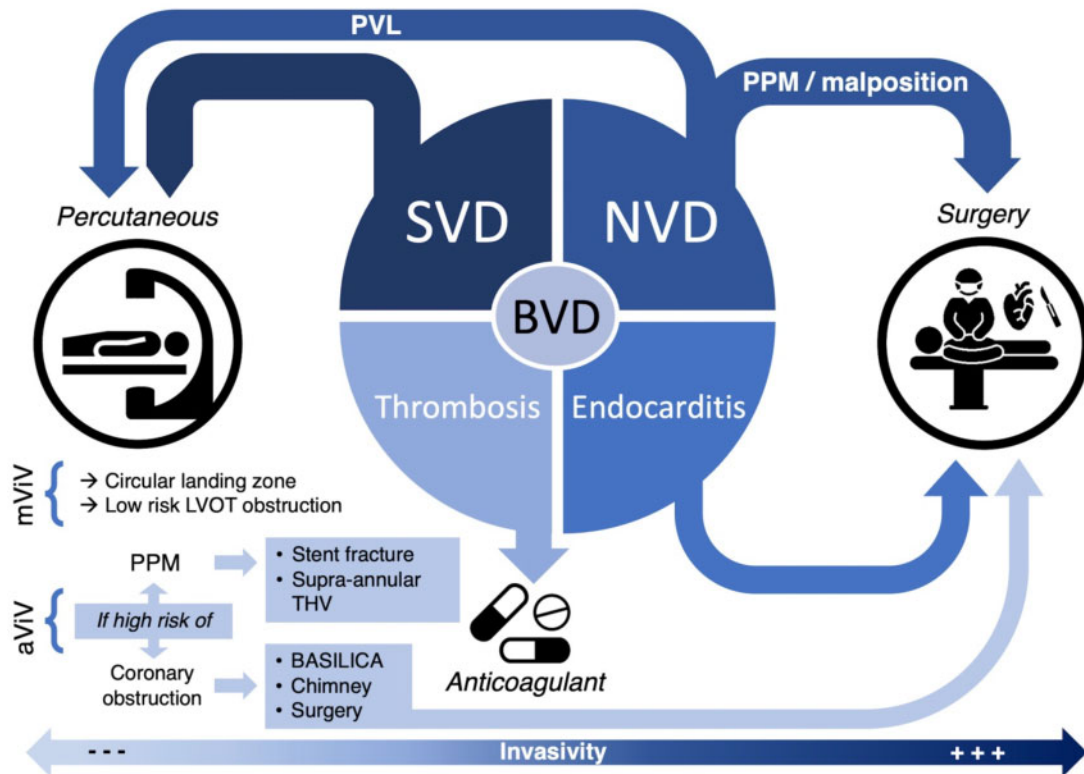
with a perioperative mortality of 7.6%, quite comparable to that of surgical reintervention. The overall 1-year survival rate of aortic ViV was 83%. Small size prostheses [ $\leq 21$  mm, hazard ratio (HR) 2.04; 95% confidence interval (CI), 1.14-3.67;  $P=0.02$ ] and baseline stenotic SVD (HR 3.07; 95% CI, 1.33-7.08;  $P=0.008$ ) were identified as predictor of mortality within 1 year.

Percutaneous treatment of degenerated mitral bioprostheses was first attempted in 2009, with a transapical and off-label use of a TAVI device in mitral position. At the beginning of 2021, the VIVID registry described also interesting data on 857 high-risk patients (mean age of 74 years old) treated with mitral ViV.<sup>17</sup> Despite a reported low rate of technical success (~40%), mainly due to restrictive MVARC definition about residual mean gradient  $\geq 10$  mmHg, the incidence of left ventricular outflow tract (LVOT) obstruction and valve migration were extremely low (1.8% and 2.8%, respectively). The 4-year overall survival rate was 62.5%.

Recently, some information has been collected about the outcomes of revalving in case of degenerated TAVI valve in aortic position. The Redo-TAVI registry showed encouraging data on 212 TAVI-in-TAVI procedures (mean age 79 years old; STS score 7%), of whom 138 with a probable THV failure after a mean of 5 years since the first intervention.<sup>18</sup> Despite 14% of significant residual gradient and 9% of residual regurgitation, periprocedural complication rate was low and 1-year survival rate was 87%.

Finally, recent data showed that in extreme cases in which a second percutaneous attempt was not achievable, surgery was feasible as well, requiring an extensive root replacement in less than 15% of cases, mostly after self-expandable THVs. However, although the overall incidence was low (<0.2% of TAVI patients), observed 1-year mortality was relatively high (~20-30%), but indication, time-to-surgery and year of explant were not associated with worse survival.<sup>19</sup>

Final judgement deriving from observational studies comparing surgical and percutaneous treatment of bioprostheses deterioration are inappropriate since TAVI patients in the first series were older and at increased risk. A Canadian propensity score matching on 558 patients revealed lower 30-day mortality in the aortic ViV group, as well as lower PM implantation rate, blood transfusions and shorter length of stay.<sup>20</sup> The 5-year survival was significantly higher with the percutaneous approach (76.8% vs. 66.8%,  $P=0.046$ ). In a recent larger US propensity score matching analysis on high-risk patients comparing 3443 aortic ViV to 3372 redo SAVR, an advantage of the percutaneous treatment in terms of 30-day mortality [odds ratio (OR) 0.41, 95% CI 0.23-0.74], morbidity (OR 0.53, 95% CI 0.43-0.72), and major bleeding (OR 0.66, 95% CI 0.51-0.85) was reconfirmed.<sup>21</sup> Similarly, analysing 62 mitral ViV vs. 59 redo SMVR, Kamioka *et al.*<sup>22</sup> showed no difference in 1-year mortality (ViV 11.3% vs. redo 11.9%,  $P=0.92$ ) and risk of LVOT obstruction (3.6% vs. 0%,  $P=0.25$ ), although mean transprosthetic gradient appeared mildly increased at follow-up in the percutaneous group (7.2 mmHg vs. 5.5 mmHg,  $P=0.01$ ).



**Figure 2** A new suggested algorithm for first-line treatment of bioprosthetic valve dysfunction. Considering the most recent encouraging evidence, we propose a new diagram for the first-line therapeutical options of BVD, in which SVD should be percutaneously treated, while NVD (PPM/prosthesis malposition) and endocarditis should undergo repeat surgery. PVL should be closed percutaneously, contrarily prosthesis thrombosis should be medically treated first. aViV, aortic valve-in-valve; BASILICA, Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction; BVD, bioprosthetic valve dysfunction; BVF, bioprosthetic valve failure; mViV, mitral valve-in-valve; NVD, non-structural valve deterioration; PPM, patient-prosthesis mismatch; PVL, paravalvular leak; SVD, structural valve deterioration.

## A new suggested algorithm

The 2017 ESC guidelines recommend surgical reintervention for treatment of significant increase in transprosthetic gradient or severe regurgitation, both for symptomatic patients (class I, level C) and asymptomatic ones at low risk (IIa, C).<sup>7</sup> However, aortic ViV should be considered during Heart Team evaluation depending on the surgical risk and size of prosthesis (IIa, C).

Given the encouraging results of ViV procedures, despite limited knowledge about long-term data, we may propose a new algorithm for the first-line treatment of surgical BVD (Figure 2). Redo surgery is mandatory in some cases such as endocarditis, prosthesis malposition/embolization, PPM, and when the risk of coronary occlusion during aortic ViV is too high even considering other transcatheter options (i.e. Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction: ‘BASILICA’; or coronary ostium stenting with ‘chimney technique’). Valve thrombosis and PVL can be treated with medical therapy and percutaneous closure devices, respectively. The recent promising results of transcatheter approach for both aortic and mitral bioprosthesis degeneration suggest to use them as first choice when approaching SVD, even for failed THVs (TAVI-in-TAVI procedure). The lower risk of LVOT obstruction and the circular landing zone

may explain the better outcomes observed with mitral ViV as compared to Valve-in-Ring and Valve-in-Mitral Annular Calcification. To avoid the risk of PPM in case of small prosthesis, supra-annular THV should be favoured, although they might impede coronary access for future interventions. As an alternative, bioprosthesis stent fracture may be also considered prior to ViV.

Theoretically, depending on the age of the patient and technical limitations, it is possible to speculate future strategies of repeated TAVI procedures (e.g. ViV for bio-SAVR degeneration after TAVI-in-TAVI failure) that could allow to avoid the use of mechanical prostheses in case of cardiac surgery or even to never have the need for surgery.

## ‘Well begun is half done’

The development of percutaneous strategies for treatment of SVD has raised new concerns about the bioprosthetic choice during a patient’s first intervention. Hypothetically, the ideal biological valve (surgical or transcatheter) should be designed not only with a large effective orifice area to provide the best haemodynamics, but also with the lowest profile possible to overcome eventual coronary obstruction issues during a future ViV/TAVI-in-TAVI procedure. In a series of 45 TAVI-in-TAVI patients undergoing post-procedural CT-scan, absence of any THV interference with coronary

accessibility was found in 8% and 33% in patients originally treated with self-expandable and balloon-expandable prostheses, respectively ( $P=0.005$ ).<sup>23</sup> Since coronary access after TAVI-in-TAVI may result challenging, the choice of THVs with intra-annular leaflet design or low commissural height and large open cells may be preferable. In other words, design will follow future perspectives.

A similar scenario could be identified in the surgical field as well. Despite the intention to improve effective orifice areas, some pericardial prostheses (i.e. St. Jude Medical Trifecta, Sorin Mitroflow, etc.) have been planned with cusps sewn outside the ring, thus increasing the risk of coronary occlusion, especially in small size aorta. To overcome the risk of PPM and to theorize the possibility for multiple ViV implants, the Inspiris Resilia, a new bioprosthesis, has been recently launched on the market by Edwards Lifesciences. The valve has been developed with an expandable stent frame, added to fluoroscopically visible marker of the prosthesis size, with the intent to facilitate forthcoming ViV procedures, especially when the risk of PPM is considerable.

## Conclusion

In the golden age of bioprosthetic heart valves, the number of patients that will face SVD is increasing. Redo surgery has always been considered the gold standard approach following BVF, but excellent results from transcatheter studies moved us to propose a new therapeutical algorithm.

However, given the absence of large RCTs, the final choice for the treatment of tissue valve dysfunction should be tailored for each patient and discussed in Heart Team, considering surgical risk and technical issues. Like in the most fascinating chess game, where the wise player can forecast the next three steps of his rival, we are now asked to move from the archaic idea of ‘instantaneous and definitive surgery’ to a more appropriate ‘life-time management’ of the bioprosthetic implanted patients.

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